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10/524,549	09/13/2005	Paolo Lusso	15358-0002	1425

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,549	LUSSO ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *1-22 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *Feb. 14, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group III, claims 23-28 in the reply filed on July 18, 2009 is acknowledged. Therefore, Claims 1-31 are pending. Claims 1-22 and 29-31 are withdrawn from consideration. Claims 23-28 are considered before the examiner.

Specification

2. The disclosure is objected to because of the following informalities: The assurance statement for the hybridoma cell line deposited in the Advanced Biotechnology Center Inter Lab Line Collection (CB ICLB) should be provided in the content of the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

4. The claim 23 is directed to non-statutory subject matter. There is no recitation of isolation or synthesis in front of the claimed antibody. Therefore, the claimed antibody could read on naturally occurring antibody in the body fluid, which are considered to be non-statutory and non-patentable subject matter within the scope of 35 U.S.C. 101. See Official Gazett, 1077 O.G. April 21, 1987. In the instate case, state of art teaches that an antibody can recognize the HIV gp120 and CD4 complex can be generated from a HIV infected individual as evidenced by Devico et al. (Virol.1995, Vol. 211, pp. 583-588, see abstract and Fig. 4). Therefore, it is recommended that the claim incorporate the claim language, " isolated or synthesized" to overcome this rejection.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for having an isolated monoclonal antibody DB-81 that is able to inhibit the HIV envelope protein mediated fusion with CD4+ T cells, does not reasonably provide enablement for using any antibody binding to a fixed cell expressing any HIV-1 envelope protein gp120 that forms a complex with soluble CD4 (sCD4) in any host cell for treating and preventing an HIV infection for any type, strains or isolates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

7. The test of scope of the enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988). These factors include the following: 1). Nature of the invention, 2). Scope of the invention, 3). State of Art, 4). Unpredictability of the filed, 5). Working example presented in the specification; 60. Guidance provided by the specification, 7). Level of skill in the art, 8). Amount of work required to fulfill the scope of the claims encompassed.

8. In the instant case, the claimed invention is a particular isolated monoclonal antibody DB-81, which can specifically recognize the T cell tropic (CXCR4 using strain) HCV envelope gp120 expressed in a CXCR4/CD4 expressing host cell that forms a complex with sCD4 complex, and using said antibody to block HV-1 infection in a mouse model. However, the scope of the claims read on using any antibody as long as it recognizes any HIV envelope protein gp120 that forms a complex with sCD4 for treating and preventing any strain or isolate of HIV infections.

9. It is well known in the art that HIV is a retrovirus that has T cell tropic (T-tropic), monocyte-tropic (M-tropic) and dual-tropic (D-tropic) strains as well as many glades and isolates. Different tropics of HIV have different structural and functional envelope proteins that recognize use different co-receptor for entering and fusing with its target cells. For example, T-tropic HIV only infect T-cell using CXCR4 co-receptor and M-tropic HIV infect monocyte via CCR5 co-receptor. HIV-1 and HIV-2 has complete envelope protein that uses different receptor/co-receptor system to infect a target cell.

10. While state of art teaches that an antibody raised with a HIV gp120 and CD4 complex can recognize the CD4 moiety and blocks membrane fusion mediated HIV envelope protein. However, the unpredictability is that 1). Such inhibition may be cell type and virus type specific. For example, one of such kind of antibody MAb55 can inhibit the syncytium formation and viral replication for T-tropic IIIB strain of HIV-1 infection in H9 cells (T cell line) as evidenced by Konopka et al. (J. Gene. Virol. 1995, Vol. 76, pp. 669-679, see entire document). HIV-1 is a retrovirus RNA virus that has many glades and variations due to the consistent mutation of the virus; and the neutralization activity of such antibody is conformation-epitope specific as evidenced by Devico et al. (Virology 1996, Vol. 218, pp. 258-263) and Kang et al. (J. Virol. 1994, Vol. 68, No. 9, pp. 5854-5862). If the HIV-1 is mutant strain, the mutant envelope protein can not be recognized by such antibody at the same level as evidenced by Sullevan et al. (J. Viol. 1998, Vol. 72, No. 6, pp. 4694-4703, see entire document, especially pages 4698-4699). Because not every antibody raised from agp120/sCD4 complex can neutralize same conformation epitope, not every such kind of antibody can get same inhibitory effect against any or all glades or variants of HIV viruses. Therefore, an antibody raised by sCD4 induced gp120 epitope exposure could be HIV serotype specific or glade specific, and virus strain specific (T tropic or M-tropic etc.)

11. In addition, regarding the claims that read on preventing HIV infection, the Applicants are reminded that using an antibody to neutralize or block virus infection is called passive immunization. It is strictly different from the passive immunization that may possibly induce an preventive immunization. In the instant case, application of an antibody to block HIV envelope protein mediated fusion with target cell, can only reduce the symptom of the disease, it can never induce any active immunization leading to prevent the HIV infection. In fact, lever of the skill in

the art for generating a vaccine or immunogenic composition can prevent HIV infection is very high and unpredictable.

12. While instant Application presents that Applicants have successfully isolated a monoclonal antibody DB-81 and demonstrate that DB-81 can block T cell tropic HIV envelope protein mediated fusions with T cell. It does not teach that such antibody can be used for preventing any kind of HIV infection. The specification does provide any guidance regarding how to use said antibody to prevent a HIV infection.

13. Given the above analysis of the factors, which the courts have determined, are critical in asserting whether a claimed invention is enabled, it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

14. Claims 23-28 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

15. In the instant case, the invention is directed to a particular monoclonal antibody, wherein the said antibody is able to block the HIV envelope protein mediated fusion. The antibody is disclosed to be produced by a particular hybridoma cell line, wherein the cell line according to the disclosure is (DB-81).

16. However, the specification does not provide a repeatable method for obtaining said antibody or hybridoma cell line, and it does not appear to be readily available material. Deposit of said hybridoma cell line would satisfy the enablement requirements of 35 U.S.C. 112. Applicant's deposit statement on specification page 45 does not indicate the extent of public availability.

17. If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that **all restrictions imposed by the depositor on the availability to the public of the deposited material will be**

irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

18. If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

(a). during the pendency of this application, access to the deposits will be afforded to one determined by the commissioner to be entitled thereto;

(b). all restrictions imposed by the depositor on the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c). the deposits will be maintained in the public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d). a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e). the deposits will be replaced if they should become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-37 CFR 1.809 for additional explanation of these requirements.

Claims interpretation: It is noted on the record, the antibody cited in the claims is interpreted by the specification as monoclonal antibody, polyclonal antibody, chimeric antibody, single chain antibody, an antibody Fab fragment, mimetic, synthetic protein, which comprises antibody binding site of an antibody and inhibits the biological activity of the antibody, eve an antiserum containing an antibody that can recognize the CD4 induced epitope of HIV-1 envelope gp120 and binds to gp120 and CD4 complex. The antibody can be used for diagnosis and therapeutic (See specification on page 28). Regarding the limitation of "a subject" cited in claim 24, because the specification does not specify and define what the subject is, the subject infected with HIV

can be reasonably interpreted as a cell or tissue because claim 24 differs for claim 25 that cites the subject is in disease or having a immune system.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 23-24 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Kang et al. (J. Virol. 1996, Vol. 68, No. 9, pp. 5854-5862).

21. Kang et al. provide a method for producing several anti-HIV –1 antibodies by immunizing the mice with a soluble CD4-gp120 complex, wherein nine such kinds of monoclonal antibodies (Mabs) can recognize several conformation-dependent epitopes near CD4 binding site of gp120 and inhibit the gp120-soluble CD4 interaction. Four of theses nine Mabs show broadly neutralize activities against multiple laboratory-adapted strains of HIV-1 (See Abstract and Table I-III) and inhibit the HIV infection. The reference therefore, anticipates the claim.

22. Claims 23-24 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Devico et al. (Virol. 1996, Vol. 218, pp. 258-263).

23. Devico et al. provide a method for producing an anti-HIV –1 antibody by immunizing the mice with a soluble CD4-gp120 complex, wherein said antibody can inhibit several glades of HIV infection (See Figs. 1-2 and Abstract). The reference therefore, anticipates the claim.

24. Claims 23-24and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Celada et al. (J. Exp. Med. 1990, Vol. 172, pp. 1143-1150).

25. Celada et al. provide a method for producing several anti-HIV –1 antibodies by immunizing the mice with a soluble CD4-gp120 complex, wherein such kinds of monoclonal

antibodies (Mabs) can inhibit the gp120-soluble CD4 interaction, block syncytia formation and HIV-1 infection (Abstract, Figs. 1-5).

26. Claims 23-24 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Konopka et al. (J. Gene. 1995, Vol. 76, pp. 669-679).

27. Konopka et al. provide a monoclonal antibody, Mab F-91-55) raised against complex of soluble CD4 and HIV-1 gp120, wherein said antibody can inhibit synsytium formation and chronically infection of HIV-1 to the target cell. The Anti-HIV –1 antibody is produced by immunizing the mice with a soluble CD4-gp120 complex, wherein such kinds of monoclonal antibodies (Mabs) can inhibit the gp120-soluble CD4 interaction and block syncytia formation as well as the virus infection (Abstract, Figs. 1-5).

28. Claims 23-24 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Sullivan et al. (J Virol. 1998 June; 72(6): 4694–4703) or Thali et al. (J Virol. 1993 Jul; Vol. 6, No. 7, pp. 3978-88) or Kwong et al. (Nature 1998, Vol. *Nature* **393**, 648-659).

29. Sullivan et al. teach that two cross-competing monoclonal antibodies, 17b and CG10 recognize soluble CD4-inducible gp120 epitopes, the envelope glycoproteins derived from both T-cell line-adapted and primary HIV-1 isolates exhibited increased binding of the 17b antibody in the presence of sCD4. The envelope protein exposed to soluble CD4 induced exposure of both 17b and CG10 antibody binding epitopes on the oligomeric envelope glycoprotein complex. They also demonstrate that the relationship between the binding of antibodies to the CD4-induced epitopes on gp120 and virus-neutralizing activity. The 17b antibody has been shown to neutralize HIV-1, especially in the presence of sCD4. The CG10 antibody can bind and neutralize the functional HIV-1 envelope glycoprotein complex in the presence of sCD4 and neutralizes the virus with the HXBc2 envelope glycoproteins with an IC_{50} of less than 1 μg of antibody per ml (See entire document, especially Fig.s 1, 4, 5, 7). They also teach that the antibody 17b or CG10 can inhibit the HIV-1 infection. Therefore, the claimed invention is anticipated by the cited reference.

30. Thali et al. or Kwong et al. teach that two monoclonal antibodies, 17b, which recognize the conformational epitopes of HIV envelope protein gp 120 induced by soluble CD4 binding to said envelope protein and inhibit the HIV-1 infection (See entire document, especially, page

3980, Fig. 102 and Abstract for Thali et al. and page 654 for Kwong et al.). Therefore, the claims are anticipated by the cited reference.

31. Claims 23-24 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by LaCasse et al. (Science 1999, Vol. 283, pp. 357-62).

32. LaCasse et al. teach a seru comprising an antibody that can recognized the CD4-gp120 complex like 17b. Because the defintion of antibody cited in the specification also includes serum comprising an antibody having same funtion for recogining the CD4/gp120 complex, and the antiserum is produced by immunizing an animal with a fixed cell expressing gp120 and CD4 togerther on the cell surface (see entire document), the cited reference anticipates the claims.

33. Claims 23-25 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Gaudain et al. (Nature Medicine, 1997, Vol. 3, pp. 1389-1393).

34. Gaudain et al. teach a monoclonal antibody IgG1b 12 and a method for using said monoclonal antibody to treat HIV infection in a mouse model, wherein the IGG 1b12 is an antibody can recognize the overlapping site for CD4 biding to gp120.

35.

Claim Rejections - 35 USC § 102

36. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

37. Claims 23 and 28 are rejected under 35 U.S.C. 102(a) as being anticipated by Dimitrov et al. (J. Human Virol. 2002, Vol. 5, No. 1 Abstract 118).

38. Dimitrov et al. describe a neutralizing antibody fragment Fab, X5, which recognize the CD4 inducible specific epitope of gp120 and binds the HIV envelope or complex comprising HIV-1 envelope protein and CD4 (Se entire abstract). Therefore, the claims are anticipated by the cited reference.

Claim Rejections - 35 USC § 102/103

39. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

40. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

41. Claims 23-25 and 28 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dimitrov et al. (US Patent No. 7,223,844B2).

42. Dimitrov et al. describe a neutralizing antibody fragment Fab, X5, and a single chain antibody that recognizes the same antigen binding site, wherein said antigen binding site is inducible by soluble CD4. The antibody fragment or single chains antibody binds the HIV envelope or complex comprising HIV-1 envelope protein and CD4 or HIV envelope, CD4 and co-receptor (Columns 9-10 and examples I-III) and block the HIV-1 envelope protein mediated fusion for both R5 and X4 strains of HIV-1. Therefore, claims 23-25 are anticipated by the cited reference.

43. Or alternative, while Dimitrov et al. do not show the data using said antibody fragment to treat HIV-1 infection, they suggests that said antibody fragment can be used for treatment of HIV infection (Column 12). Hence, the claimed invention as a whole is prima facie obvious absence unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 6:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bao Qun Li
09/28/2007

BAOQUN LI, MD
PATENT EXAMINER